ACMD

Advisory Council on the Misuse of Drugs

Consumer Cannabidiol (CBD) products

December 2021

Contents

1. Introduction

1.1. Consumer Cannabidiol (CBD) products (i.e. CBD products which are not licensed medicines and which are available to purchase online or on the high street) are sold for their potential to produce 'wellbeing' benefits (Chesney, McGuire, Freeman, Strang, & Englund, 2020). CBD is a non-controlled cannabinoid present in *Cannabis* plant extracts. Currently the most commonly sold CBD product is CBD oil, however, the range of products containing CBD is expanding and includes food supplements, drinks, cosmetics and liquids for vaping. Consumer interest in CBD is growing (European Monitoring Centre for Drugs and Drug Addiction, 2019).

1.2. At present the CBD within these products is derived primarily from the plant *Cannabis*. Due to difficulties in isolating CBD from other cannabinoids, consumer CBD products also contain varying amounts of *trans*-delta-9-tetrahydrocannabinol-C5 (Δ^9-THC) and other cannabinoids present in *Cannabis* that are controlled under the Misuse of Drugs Act 1971 (MDA).

1.3. In January 2021, the Home Office stated its intention to establish a legal framework for consumer CBD products in a commissioning letter to the ACMD.

1.4. The ministerial commission has sought advice from the ACMD, specifically on:

1.4.1. The maximum dose for any non-negligible effect for Δ^9-THC, THCV and CBN and the cannabinoid Δ^9-THCA-A;
1.4.2. Whether such products would be liable to be abused or have ill-effects;
1.4.3. Whether the controlled substances, in practice, can be recovered from such products;
1.4.4. The current analytical capability to test for cannabinoid content;
1.4.5. How the exempt product definition in the MDR may be amended to apply only to diagnostic equipment, or for scientific research, as originally intended. (Note: this part of the commission will be considered in a separate piece of advice).

1.5. To respond to this commission, the ACMD formed a Working Group who have reviewed the literature, consulted with industry and analytical laboratories, and issued a public call for evidence.

1.6. This report will not evaluate the effectiveness of CBD products. Nor will it re-evaluate the potential harms of any of the controlled cannabinoids, nor make comment about their classification or schedule. This report will consider the dose at which cannabinoids have no detectable psychoactive effect on humans (i.e. for the purposes of this report, dose means amount in grams), the analytical capabilities to test for these cannabinoids, and the feasibility of production of consumer CBD products with low levels of controlled cannabinoids. The intention being to give consideration to consumer CBD products derived from extracts of *Cannabis* rather than to plant products.

2. Background

2.1. Plants of the genus *Cannabis* contain multiple naturally occurring cannabinoids that are referred to as 'phytocannabinoids'. Twelve phytocannabinoids are controlled under the MDA. The main psychoactive phytocannabinoid is Δ^9-THC, commonly known as THC, which acts as a partial agonist at the cannabinoid type-1 receptor (CB_1 receptor) in the brain. For a review of the control status of phytocannabinoids, please refer to Table 1 from ACMD's 2016 report on Phytocannabinoids (ACMD, 2016).

2.2. Phytocannabinoids such as cannabidiol (CBD), that have low affinity for the orthosteric (agonist) binding site on the CB_1 receptor, are not controlled. CBD has been reported to act as a negative allosteric modulator at CB_1 and CB_2 receptors, reducing the response to agonists such as Δ^9-THC (Laprairie, Bagher, Kelly, & Denovan-Wright, 2015), (Tham, et al., 2019).

2.3. The CBD that is used in consumer products is mainly extracted from *Cannabis* flower and leaves and the resulting product referred to as 'CBD isolate'. Whilst trying to maximise the CBD content of the isolate it still contains other phytocannabinoids including those that are controlled. Throughout this report 'CBD isolate' will refer to this extracted product. In the UK, a Schedule 1 controlled drugs licence is required to grow *Cannabis*, irrespective of the THC content of the plant. To lawfully use the controlled parts of the plant (the flower and leaves) licensing permissions to enable possession, production and potentially supply of 'Schedule 1' material would be required as the possession of harvested material from controlled parts of the plant would be unlawful without a licence.

2.4. CBD can also be produced by chemical synthesis (Jung et al., 2019). As the popularity of consumer CBD products increases, the demand for synthetic CBD is likely to increase and improved methods developed (Bloemendal et al., 2021). Commercially produced synthetic CBD may however still be contaminated with Δ^9-THC (Grubb, 2020). The Working Group therefore decided that for the time being the regulations relating to the levels of controlled phytocannabinoids in CBD consumer products should apply whether the origin of the CBD is by extraction from the *Cannabis* plant or by chemical synthesis.

2.5. To obtain a controlled drug from another country an import licence must be obtained from the Home Office. This is to enable the UK government to keep records of such transactions for reporting purposes and remain compliant with their international obligations to the International Narcotics Control Board (INCB).

2.6. Within the MDR there is an exempt product definition that excludes products from control if they meet all of the 3 criteria required for exemption (UK Legislation, 2001). Companies which market consumer CBD products often claim their products meet all of the 3 criteria and are therefore exempted from control under the MDA. This commission also asked for the ACMD to reword the exempt product definition

to apply only to diagnostic equipment or for scientific research, thereby unambiguously excluding consumer products and any products intended for human consumer other than in scientific research – this will be covered by a separate piece of advice.

2.7. The industrial hemp industry in the UK, under the requisite licence, grows low-Δ^9-THC content *Cannabis* or 'hemp' for fibre and seed (under the stipulations of the Industrial Hemp Licence all controlled parts of the plant must be destroyed). The farmed components have various industrial uses, such as the processing of the seeds to make cold pressed hemp seed oils (as distinct from CBD oil) and using the fibre to produce clothing or rope.

2.8. Hemp production for use of the uncontrolled fibre and seed is considered under a different policy and licensing regime to a *Cannabis* Cultivation licence for use of the controlled parts of the plant which are required for CBD production. There is a misconception amongst some members of the consumer CBD product industry that consumer CBD products are legal if they contain less than 0.2% Δ^9-THC. This misunderstanding may arise from an incorrect interpretation of the wording within the Misuse of Drugs (Licence Fees) Regulations 2010. A licenced grower of hemp must only cultivate a *Cannabis* strain that is on the approved seed type list and contains less than 0.2% Δ^9-THC to meet the requirements of that licence. This licence only allows for the use of uncontrolled parts of the *Cannabis* plant and therefore should not be used to cultivate material for any other purpose including creating CBD isolate.

2.9. The relatively unregulated nature of the consumer CBD product market has meant that the actual levels of Δ^9-THC in different products from different suppliers vary dramatically. A Defence Science and Technology Laboratory (Dstl) investigation into forty-three commercial CBD products available in the UK found sixteen (37%) contained more than 5 mg of Δ^9-THC (Defence Science and Technology Laboratory report, 2020a). For context 5 mg Δ^9-THC is one standard THC unit – a low dose that can produce mild psychoactive effects similar to a standard alcohol unit (Freeman & Lorenzetti, 2020). Similar variability in the CBD and Δ^9-THC content of consumer CBD products available in the UK, Europe and the USA have been reported in the scientific literature (Pavlovic, et al., 2018), (Lachenmeier, et al., 2019), (Dubrow, et al., 2021), (Liebling et al., 2020).

2.10. Health food shops in the UK currently sell CBD capsules and edible products ranging from 5 to 20 mg per dose, and oils and sprays from 2 to 8 mg per dose (Chesney, McGuire, Freeman, Strang, & Englund, 2020). The Food Standards Agency recommended the level of safe consumption to be 70 mg/day (Food Standards Agency, 2020).

2.11. The ACMD has consulted with the National Police Chiefs' Council (NPCC), who reported that there has been no evidence to date of diversion of consumer CBD

products or extraction from such products of Δ^9-THC or other controlled phytocannabinoids. The Working Group highlights that in addition to the lack of evidence, it would be highly unlikely that consumers would seek to use CBD products for the psychoactive effects of Δ^9-THC, due to the very low levels of Δ^9-THC present in such products.

2.12. In this report, levels of phytocannabinoids at which a user may experience noticeable psychoactive effects will be discussed. Within the scientific literature the term 'intoxication' would typically be used, with the term 'psychoactive' having multiple different uses and the term 'psychotropic' having medicinal connotations. Within legislation the UN use the term 'psychotropic' in their Convention on Psychotropic Substances 1971, whereas the UK have used 'psychoactive' in the Psychoactive Substances Act 2016 (PSA). Whilst 'intoxication' might be scientifically correct, it has negative connotations in the public sphere and so the report throughout will use the term 'psychoactive' to refer to the effects of these drugs as it most closely aligns with other UK legislation.

2.13. When defining the levels of substances within products there are different measures that can be used. In this report the levels of phytocannabinoids within a product (no matter what product) are given in the form of the weight in grams or the weight of the substance as a percentage of the weight of the total product (i.e. % w/w). For consistency, when referring to products that are liquids this report will still use % w/w, not weight by volume (i.e. % w/v). Amongst consumer CBD product producers it is common practice when giving the levels of controlled phytocannabinoids such as Δ^9-THC in CBD products to indicate the amount of Δ^9-THC as a percentage of the weight of CBD in the product (i.e. the ratio of % weight Δ^9-THC to weight of CBD). However, to avoid any confusion, this report will only use weight of the substance as a percentage of the weight of the product in which it is contained unless specifically stated otherwise.

3. Controlled Phytocannabinoids

3.1. Phytocannabinoids are controlled using generic definitions within the MDA. The ACMD's Phytocannabinoids report (ACMD, 2016) identified 12 phytocannabinoids that would be considered controlled under the MDA. These are detailed in Annex D.

3.2. Since the last review of phytocannabinoids (ACMD, 2016) two further analogues substituted at the 3-position of *trans*-(-)-Δ^9-THC with slightly more extended alkyl chains have been described (tetrahydrocannabiphorol [THCP, 3-heptyl] (Citti, et al., 2019) and tetrahydrocannabihexol [THCH, 3-hexyl] (Linciano, et al., 2019). Their psychoactivity in humans has not been reported, although structure-activity considerations suggest that they are likely to have activity as CB_1 agonists. The fact that they have only recently been identified may be taken as an indication of their low abundance.

3.3. While there is some evidence from human and animal studies that CBD can attenuate or exacerbate the behavioural and cognitive effects of Δ^9-THC, these observations have not been consistently reported and may only occur at doses of CBD higher than those available from consumer CBD products (Englund, et al., 2013). Furthermore, there is at present no firm evidence for minor phytocannabinoids or terpenoids present in preparations of *Cannabis* acting synergistically to enhance the effects of Δ^9-THC nor interacting with CBD to elicit an acute psychoactive effect (Chesney, McGuire, Freeman, Strang, & Englund, 2020), (Finlay, Sircombe, Nimick, Jones, & Glass, 2020), (Santiago, Sachdev, Arnold, McGregor & Connor, 2019), (Cogan, 2020).

Precursors

3.4. In this report the term 'precursor' is used simply to describe chemical compounds in the *Cannabis* plant that are converted naturally into phytocannabinoids. This does not come under precursor chemical licencing controls of illicit synthesis of controlled drugs.

3.5. The *Cannabis* plant generates several acidic phytocannabinoid precursors (Wang, et al., 2016). In fresh *Cannabis* Δ^9-THC, CBD, and CBC exist as their acidic (carboxylated) precursors (Wang, et al., 2016), (Tahir, Shahbazi, Rondeau-Gagné, & Trant, 2021). Two Δ^9- THC precursors have been identified in the plant (2-carboxyl Δ^9-THC, referred to as Δ^9-THCA-A, and 4-carboxyl Δ^9-THC, referred to as Δ^9-THCA-B). The more abundant form being Δ^9-THCA-A which has only weak agonist activity at CB_1 and CB_2 receptors (McPartland, et al., 2017). Hereinafter, unless specifically identified, these two precursors are combined and referred to as Δ^9-THCA. There is no indication of Δ^9-THCA being converted to Δ^9-THC to any significant degree within the body after ingestion.

3.6. Conversion of acid precursors to corresponding THC analogues is achieved by heating. Whilst precursor acids can be converted to phytocannabinoids at temperatures of less than 100 ^oC, a much longer duration is needed for this

conversion to occur without heating (Wang, et al., 2016). Conversion is more rapid at elevated temperatures. It is anticipated that at room temperature, conversion of THCA to THC analogues is negligible.

3.7. Measurements intended to indicate the psychoactive potency of *Cannabis*-derived materials usually include both the amount of Δ^9-THC and the amount of Δ^9-THCA to address the potential for conversion of Δ^9-THCA to Δ^9-THC in storage and by heating. The total Δ^9-THC content (Δ^9-THC plus Δ^9-THCA) is calculated within US legislation by applying a conversion factor of 0.877 to allow for the percentage of the weight of Δ^9-THCA, which is lost in the decarboxylation process based on the molecular weights of the two materials (US legislation, 2018).

3.8. Legally precursors are not controlled within the MDA or MDR, however, in this report we will suggest limits apply to them when in CBD products.

Interconversion

3.9. Phytocannabinoids are structurally related compounds with the potential in some cases for chemical conversion from one to another. With the exception of precursor acids (discussed above) it is very unlikely that most non-psychoactive phytocannabinoids are converted into psychoactive ones except under laboratory conditions.

3.10. CBD can be converted to Δ^9-THC under acid and heat conditions or utilising more specialised laboratory reagents to achieve the cyclisation. Whether such conversion occurs in the acidic contents of the stomach following oral administration has been the subject of much experimentation and debate (Golombek, Müller, Barthlott, Sproll, & Lachenmeier, 2020). At present no definitive answer is available.

3.11. Δ^9-THC can be converted to cannabinol-C5 (CBN). This may be relevant to the storage of CBD products, especially when they are exposed to air and humidity (Pavlovic, et al., 2018), (Citti, et al., 2019). CBN is less potent than Δ^9-THC in producing psychoactive effects (Perez-Reyes M., Timmons, Davis, & Wall, 1973) and has been reported to be present at lower levels than Δ^9-THC in CBD products (Pavlovic, et al., 2018), (Defence Science and Technology Laboratory report, 2020b).

3.12. In addition to the oral route of administration, some consumer CBD products may be inhaled following vaporization or smoking. These include CBD vape-liquids and herbal CBD products such as "*Cannabis* light" (Cas, et al., 2020). Inhalation of Δ^9-THC produces similar psychoactive effects following either vaporization or smoking (Abrams, et al., 2007) (Newmeyer, Swortwood, Abulseoud, & Huestis, 2017). In a recent study, it was reported that under oxidative conditions CBD could be converted to Δ^9-THC by heating (Czégény, et al., 2021). However, it is not known at

present if CBD would be converted to Δ^9-THC when dissolved in liquids containing glycerine or propylene glycol which are commonly used for vaping.

Psychoactivity

3.13. The ACMD's Phytocannabinoids report (ACMD, 2016) found sufficient evidence to determine the psychoactivity of Δ^9-THC, delta-8-tetrahydrocannabinol (Δ^8-THC) and CBN. It was unsure about the psychoactivity of delta-9-tetrahydrocannabivarin (THCV). For the remaining 8 controlled phytocannabinoids there was not sufficient evidence to determine psychoactivity. Here the potential threshold dose that is unlikely to produce any psychoactive effect for Δ^9-THC, Δ^8-THC, THCV and CBN, is considered.

3.14. Most phytocannabinoid research has focused on Δ^9-THC or CBD, with limited investigation of other phytocannabinoids, such as THCV, Δ^8-THC or CBN.

Δ^9-THC

3.15. Experimental psychopharmacology studies in humans have found that acute administration of Δ^9-THC can produce psychoactive effects at single oral doses as low as 2.5 – 5 mg (Haney, 2007), (Ballard & Wit, 2011), (Chesher, Bird, Jackson, Perrignon, & Starmer, 1990), (Beal, et al., 1995), (Beal, et al., 1997).

3.16. It has been reported that single inhaled doses of Δ^9-THC as low as 2 mg can produce psychoactive effects (Zuurman, et al., 2008), (Klumpers, et al., 2012). There is a lack of studies testing the effects of single inhaled doses of Δ^9-THC lower than 2 mg.

3.17. The peak level of subjective effects from Δ^9-THC are similar for oral, smoked and vaporized administration of the same dose of Δ^9-THC among infrequent *Cannabis* users, but oral administration results in slower onset and longer duration of effects (Newmeyer, Swortwood, Abulseoud & Huestis, 2017).

3.18. There is a lack of studies relating to the effects of lower doses of Δ^9-THC in healthy subjects.

Δ^8-THC

3.19. Whilst the ACMD Phytocannabinoids report found Δ^8-THC to be psychoactive, there was not sufficient evidence in humans to establish a threshold dose for psychoactive effects. However, there is a single report from the 1970s that suggests the potency both orally and intravenously of Δ^8-THC is similar to Δ^9-THC (Hollister & Gillespie, 1973).

THCV

3.20. The disputed potential psychoactivity of THCV motivated the 2016 report into phytocannabinoids (ACMD, 2016). That report concluded that the psychoactivity of THCV had not been determined.

3.21. Two studies found that a single oral dose of 10 mg THCV produced no detectable subjective effects (Tudge, Williams, Cowen & McCabe, 2015), (Rzepa, Tudge & McCabe, 2016). When administered orally for five sequential days, 10 mg THCV was also found to be indistinguishable from matched placebo (Englund, et al., 2016).

CBN

3.22. Oral administration of CBN produced no psychoactive effects at a dose of 50 mg (Karniol, Shirakawa, Takahashi, Knobel & Musty, 1975). A study comparing single intravenous doses of Δ^9-THC, CBN and CBD found that the dose of CBN required to produce subjective psychoactive effects was over 10-fold higher than that for Δ^9-THC (Perez-Reyes M., Timmons, Davis & Wall, 1973).

Summary

3.23. While the precise thresholds for psychoactive effects from Δ^8-THC, THCV and CBN may not be possible to estimate, it can be concluded with reasonable certainty that the threshold dose for THCV and CBN would be substantially higher than the threshold for Δ^9-THC, with that for Δ^8-THC being unknown.

3.24. *Cannabis* in its various forms (leaf, flower, resin and extracts) is an exceptionally complex matrix comprising hundreds of phytochemicals, of which the cannabinoids (CBD, Δ^9-THC, CBG, CBC, Δ^8-THC, CBN, THCV) are also extremely variable in terms of their concentrations (Kinghorn, Falk, Gibbons & Kobayashi, 2017). However, while the concentration of Δ^9-THC in *Cannabis* plant samples may be typically in the region of 15-20% the other controlled phytocannabinoids are present in very low concentrations e.g. <0.1% for THCV; <0.1% Δ^8-THC; <1% for CBN (Chandra, et al., 2019).

3.25. The Working Group concluded that it is very unlikely that plant-derived consumer CBD products would contain sufficient controlled phytocannabinoids (apart from Δ^9-THC) to produce any pronounced psychoactive effects unless they were purposely added to the product.

4. Analytical Techniques

4.1. Measurement of levels of controlled phytocannabinoids in consumer CBD products comprises three stages.

4.1.1. Extraction of the phytocannabinoids from the product matrix into a suitable solvent compatible with the analytical method to be used.

4.1.2. Separation of the phytocannabinoids from each other and from other non-phytocannabinoid compounds in the extract. This is normally performed by gas chromatographic (GC) or liquid chromatographic (LC) techniques. GC involves heating the sample and this will convert thermally labile precursor acids to active phytocannabinoids. LC does not involve high temperatures and so preserves thermally labile compounds.

4.1.3. Detection and quantification of the amount of each phytocannabinoid. There are various techniques used for detection which differ in their sensitivity (see Annex C). Quantification of the amount of each phytocannabinoid present requires comparison with certified standards of each compound.

4.2. The commonly used methods of separation and detection have recently been reviewed by the Defence Science and Technology Laboratory (Defence Science and Technology Laboratory report, 2020b). The advantages, disadvantages and Limit of Quantification (LoQ) of each technique are summarised with descriptions in Annex C. Mass spectrometry (MS) or tandem mass spectrometry (MS-MS) offer the most sensitive methods for quantification but are also the most expensive to perform.

4.3. Accurate measurement of phytocannabinoids depends both on the resolution of the separation method and the selectivity of the detection method. GC with flame ionisation detection or LC with UV detection have low specificity and therefore if Δ^9-THC and other trace phytocannabinoids are not completely separated from one another and from other substances in the extract then coelution with interfering substances may increase the detector response causing an overestimate of the analyte concentration. This can largely be overcome by use of a more selective detector such as MS or MS-MS which can usually be set to only respond to the analyte of interest even if it coelutes with another substance.

4.4. In order to comply with any specified limits for the concentrations of Δ^9-THC and other controlled phytocannabinoids in consumer CBD products the analytical method must be capable of detecting and quantifying these substances at concentrations below the specified limits. Using a method with insufficient sensitivity and obtaining a negative result does not prove that the phytocannabinoid is not present.

Testing capability and reliability

4.5. In early 2021, an inter laboratory comparison trial (referred to as a 'ring-trial') sponsored by a number of government departments and devolved administrations, and co-ordinated by the Government Chemist's Team was run to assess the capability of analytical laboratories (based in UK and elsewhere) to undertake the analysis of consumer CBD products for the presence of CBD and other phytocannabinoids, including Δ^9-THC, Δ^9-THCA-A, Δ^8-THC, CBN and THCV (Government Chemist's Team, 2021). While the full report is available online, below we provide a brief summary.

4.5.1. A set of three commercially available consumer CBD products, an oil, a spray and a body wash, was circulated to the participating laboratories and the analytical findings returned were evaluated. The participating laboratories used a variety of analytical techniques and protocols. The trial established that while the majority of the laboratories were able to produce satisfactory results for the amount of CBD in the products supplied, the results for other controlled phytocannabinoids, which were present in the samples at lower concentrations, were more varied. A number of participating laboratories were either unable to detect or to reliably quantitate some or all of the other phytocannabinoids of interest.

4.5.2. The trial identified the need to apply advanced analytical techniques, such as LC-MS/MS, in order to achieve the sensitivity necessary to quantitate accurately the controlled phytocannabinoids present in CBD products. The use of appropriate internal standards, such as stable isotope labelled versions of the target analytes, was recommended in order to improve the reliability of quantitation.

4.5.3. Application of the sensitive methodology suggested by the ring-trial evaluation, preferably combined with independently assessed quality assurance measures such as proficiency testing and accreditation, would improve the analytical reliability that would be necessary to underpin any regulations developed to limit the levels of controlled phytocannabinoids in CBD products.

4.6. When analysing trace components of complex materials, matrix effects, such as those caused by other components co-eluting from the separation stage of the analysis with the target species, can be problematic. Therefore, the levels of accuracy achieved in laboratories (such as within the Government Chemist's ring trial (Government Chemist's Team, 2021) may differ from the theoretical maximum of these techniques as reviewed in the Dstl report (Defence Science and Technology Laboratory report, 2020b).

4.7. The extraction and analysis of trace amounts of phytocannabinoids in consumer CBD products is technically challenging. The extraction method and parameters used for the method of analysis need to be optimised for each type of product; there is no single method that can be used effectively for all products.

4.8. The product composition or matrix (this may include oils, fats, sugars, gums, particulates etc) can reduce the efficiency of extraction of the controlled phytocannabinoids. The exact chemical composition of the product matrix may not be known and therefore it may only be possible to simulate approximately the matrix with a similar matrix (for matrix matching). These sample matrix effects necessitate the use of extraction methods optimised for each CBD product and the use of an internal standard to compensate for any reduction in extraction efficiency.

4.9. The CBD isolate used in the production of consumer CBD products contains many other compounds present in trace amounts which may interfere with the detection of Δ^9-THC and other controlled phytocannabinoids. CBD itself has a chemical structure closely related to those of the controlled phytocannabinoids but is present at a concentration several thousands of times higher, which makes it difficult to detect the controlled phytocannabinoids at trace levels.

4.10. Δ^9-THC and other controlled phytocannabinoids at trace levels are also susceptible to chemical degradation by heat and oxidation during the process of extraction and analysis.

4.11. In addition, analytical uncertainty tends to increase as the concentration of the analyte being measured decreases (the 'Horwitz trumpet' effect).

4.12. Detection and quantification of low levels of Δ^9-THC and other controlled phytocannabinoids in the presence of CBD within a variety of matrices is analytically challenging and use of inadequate analytical procedures could lead to erroneously negative findings.

4.13. Quality assurance techniques such as use of appropriate reference materials, analysis of control samples and participation in proficiency testing can all help to ensure that analyses are valid, and results are dependable. However, the most effective route to be able to demonstrate analytical competence and reliability of results is for the analytical processes to be accredited to the international standard, ISO 17025, by means of third-party assessment. This addresses aspects such as the qualifications, training and experience of the staff, use of appropriate and validated testing procedures and equipment which is properly calibrated and maintained, adequate quality assurance procedures, proper sampling practices, traceability of measurements to national standards, accurate recording and reporting procedures and the suitability of testing facilities.

4.14. Laboratories assessing compliance would need to be accredited to the ISO standard. Producers should use laboratories which hold that accreditation to perform their quality assessment testing.

Phytocannabinoid reference standards

4.15. Chemical reference standards are well characterised substances which can be used as points of comparison to support identification and quantitation of target analytes. Reference standards produced by suppliers certified to the relevant International Standard (ISO Guide 34) provide reliable and traceable reference points.

4.16. Major suppliers of drug-related chemical reference materials provide certified reference standards for the most common phytocannabinoids of analytical interest such as: Δ^9-THC, Δ^9-THCA-A, Δ^8-THC, THCV, CBD, CBN and CBC. Product ranges include stable-isotope labelled versions of THC, CBD and CBN. However, currently standards are not commercially available for all of the controlled phytocannabinoids (See Annex D).

5. Interpretation of findings

5.1. The purpose of this report is to recommend appropriate limits on the level of controlled phytocannabinoids within consumer CBD products. It is common practice for the weight of phytocannabinoids to be reported as a percentage of the amount of CBD present. However, the range of consumer products derived from *Cannabis* is rapidly changing, with new products coming to market for the consumption of other uncontrolled phytocannabinoids such as cannabichromene (CBC) and cannabigerol (CBG). To future proof any legislation, the recommended limits of controlled phytocannabinoids in this report are given as weight in grams or weight of phytocannabinoid as a percentage of the weight of product.

5.2. In a review of the open literature on the analysis of CBD consumer products Dstl collated data (Figure 1) demonstrating a wide range of Δ^9-THC content in products (Defence Science and Technology Laboratory report, 2020b).

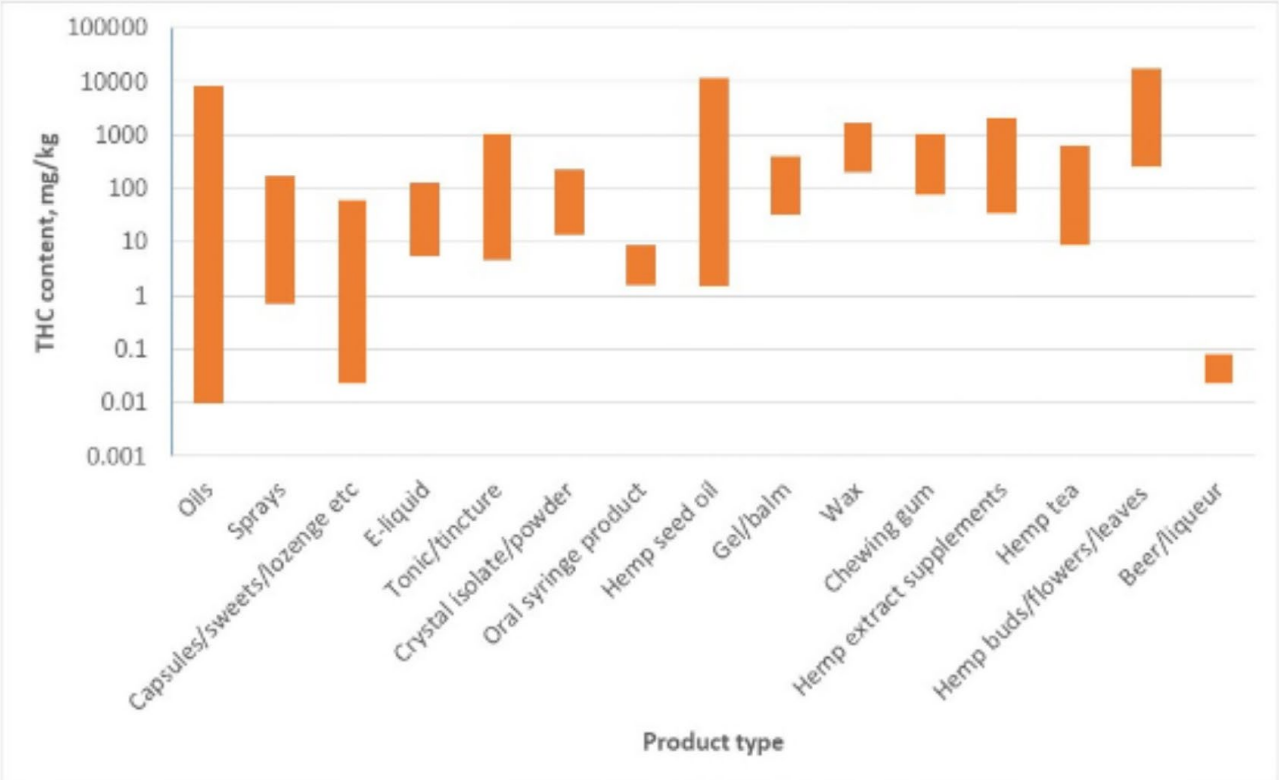


Figure 1: Bar chart with logarithmic y-axis showing the ranges of Δ^9-THC content in different CBD and hemp consumer products reported in the open literature. The top and bottom ends of each bar represent the maximum and minimum quantities detected in the samples. Figure reproduced from Defence Science and Technology Laboratory, 2020b © Crown Copyright 2020.

5.3. The variation in the Δ^9-THC content within the same types of products (Figure 1) likely reflects the unregulated nature of the market.

5.4. From the consultations with industry it is the Working Group's understanding that typical CBD isolate used in the production of CBD products contains 0.02-0.03% (% w/w Δ^9-THC to CBD i.e. not Δ^9-THC as a % weight of product). CBD isolate containing lower amounts of Δ^9-THC are commercially available (e.g. with 0.005-0.007% Δ^9-THC to CBD) but these are more expensive to produce.

Controlled phytocannabinoids for which levels should be set

5.5. When considering which phytocannabinoids should have limits set the following factors were taken into account:

5.5.1. Levels (relative) found in *Cannabis* preparations/*Cannabis* plants.

5.5.2. The potential psychoactive potency of each phytocannabinoid.

As described in Chapter 3, the controlled phytocannabinoids other than Δ^9-THC are either present in insufficient quantities or are of such low potency that they can be considered not to exert any psychoactive effect when present in consumer CBD products. Therefore, the Working Group concluded that it was appropriate to set specific limits for the content of Δ^9-THC and its precursors Δ^9-THCA-A and Δ^9-THCA-B in consumer CBD product.

5.6. Δ^9-THC and Δ^9-THCA (i.e. Δ^9-THCA-A and Δ^9-THCA-B) are present in CBD products. Δ^9-THCA can convert to Δ^9-THC with heat. Therefore, to control the quantity of Δ^9-THC the limit should also take into account Δ^9-THCA. These two compounds can either be measured in a combined manner (when analysis is performed using a technique that involved heating such as gas chromatography) or separately (when using techniques like liquid chromatography). When measured separately, within US legislation (US legislation, 2018), the amounts of each are combined to give the total possible Δ^9-THC content taking into account their relative molecular weights using the following formula

$$\Delta^9\text{-THC}_{total} = \Delta^9\text{-THC}_{weight} + (0.877 \times \Delta^9\text{-THCA}_{weight}).$$

Equation 1: Formula for total Δ^9-THC content

5.7. However, not setting any limit for the other controlled phytocannabinoids could set a precedent whereby a CBD product to which any of these other controlled phytocannabinoids had been added (i.e. spiked) might be considered legal. To prevent this possibility, it was agreed that the maximum level of each controlled cannabinoid should be the same as Δ^9-THC + Δ^9-THCA.

5.8. Whilst the other controlled cannabinoids do have precursor acids, they are present in low amounts. The need to measure these could become burdensome upon producers. Therefore, it was decided not to recommend controlling these at present.

Determining a maximum dose of Δ^9-THC that would not produce a psychoactive effect

5.9. In considering what would be the appropriate level for Δ^9-THC in commercial CBD products we first considered the lowest dose of Δ^9-THC that would produce any adverse effects (LOAEL). In the written submissions received to our Call for Evidence and in international food regulations the recommended LOAEL for Δ^9-THC ranges between 2 – 5 mg/day. This agrees with the experimental studies on psychoactive properties described in paragraphs 3.15 – 3.18.

5.10. The remit of this report was to recommend a 'low', trace level for the controlled phytocannabinoids in consumer CBD products under the MDA and so consideration was given to the maximum dose of Δ^9-THC that would be unlikely to produce any psychoactive effect (i.e. elevation of mood or 'high'). The Working Group consider that a Δ^9-THC dose of 1 milligram (mg) was unlikely to produce significant psychoactive effects.

5.11. A major challenge for recommending a single dose level for Δ^9-THC is how applicable it is to consumer CBD products consumed by different routes of administration– oromucosal, oral, inhalation, topical – where the bioavailability, rate of absorption and peak levels may be different. In studies of the psychoactive effects produced by the same dose of Δ^9-THC administered orally or by inhalation the peak level of effect was observed to be comparable between the two routes (Ohlsson et al.); infrequent users in (Newmeyer, et al.). In the absence of more definitive studies on the maximum dose of Δ^9-THC that would be unlikely to produce any psychoactive effect when given by different routes of administration the Working Group propose that 1 mg should apply to all consumer CBD products.

5.12. There is very limited information available on whether young people are more or less sensitive to the psychoactive effects of Δ^9-THC. In one study comparing the acute effects of *Cannabis* in adolescent (16–17 years old) and adult (24–28 years old) male *Cannabis* users, it was reported that after inhaling vaporized *Cannabis*, adolescents reported fewer psychoactive effects than adults (Mokrysz et al).

5.13. The ACMD has consulted with the National Poisons Information Service who report that for consumer CBD products in general episodes of toxicity involving children are very rare.

5.14. Two additional uncertainty factors were then applied (Table 1):

- The first of 10 (to account for differences in age, body size, individual variation in response) and,
- a second of 2 (to take account of variations in use or concurrent use of more than one product).

5.16 No uncertainty factor has been applied to account for the possibility of CBD along with other cannabinoid and terpenoid compounds that may be present in CBD products acting to enhance the actions of Δ^9-THC. Studies to date have not provided compelling evidence for such an interaction (Chesney, McGuire, Freeman, Strang, & Englund, 2020), (Finlay, Sircombe, Nimick, Jones, & Glass, 2020), (Heblinski, et al., 2020), (Santiago, Sachdev, Arnold, McGregor, & Connor, 2019), (Cogan, 2020).

Calculation	Δ^9-THC Total amount	Δ^9-THC Total amount (g)
Non psychoactive dose	1 mg	1×10^{-3}
Reduction by 10x (to account for variability in age, body size, individual variation in response)	100 µg	1×10^{-4}
Further reduction by 2x (to take account of variations in use or concurrent use of more than one product)	50 µg	5×10^{-5}

Table 1: Calculation of recommended maximum Δ^9-THC dose.

Setting the defined trace percentage for Δ^9-THC in consumer CBD products

5.17. Three approaches to setting the limits for the level (concentration) of controlled phytocannabinoids in consumer CBD products were considered, along with their advantages and disadvantages.

- Setting a level that would apply to all consumer CBD products
- Setting a level as a percentage of CBD content
- Setting different levels for different CBD products

5.18. **Setting a level for controlled phytocannabinoids** that would apply to all consumer CBD products has the advantage of being the simplest to do in legislation. However, it has practical disadvantages.

5.18.1. Due to the differences in product matrix and difficulties in extracting phytocannabinoids from different products (see Chapter 4: Analytical Techniques) a limit that is practical to test in one product such as a drink might not be practical in another such as oil or food.

5.18.2. There are significant differences in the weight of a typical single serving of different products (here the terms ‘unit of consumption’ and ‘single serving’ are used to refer to a typical quantity consumed in one occasion, such as drops of oil, capsule, bottle or can of drink, or a chocolate bar). To meet the limit set, producers of products for which a single serving is of low weight (e.g. oils, capsules) would therefore have to use initial CBD isolate of higher purity (lower levels of Δ^9-THC) than producers of products where the single serving is of higher weight (e.g. chocolate bar, drinks) if the final concentration of Δ^9-THC has to be under the limit set. This would have significant financial implications for manufacturers of CBD products that have a low single serving weight as they would have to use CBD isolate of lower Δ^9-THC content (see paragraph 5.4).

5.19. **Setting a level for controlled phytocannabinoids as a percentage of CBD content** has the advantage of being practical as the ratio of controlled phytocannabinoid to CBD content could be determined in the initial isolate. However, this method presents three difficulties.

5.19.1. A product with large quantities of controlled phytocannabinoids could be produced by increasing the level of CBD.

5.19.2. Separate legislation would be required to limit the content of controlled phytocannabinoids in any new consumer products containing uncontrolled phytocannabinoids such as CBC or CBG.

5.19.3. In calculating this ratio of Δ^9-THC to CBD the error in the estimations of each would be compounded when taking the ratio.

5.20. **Setting levels for different types of product** individually allows for variations in weight of single servings of different products and avoids the problems that arise when setting one limit across all products as outlined above. Setting levels for the controlled phytocannabinoids avoids issues of setting the limit relative to the CBD content, though it does mean considerations have to be made to what is feasible regarding the sensitivity of the methods used to measure low concentrations of phytocannabinoids. The Regulations would be more complex and require product by product evaluation but would provide a framework that can be used in future for novel products that will require market authorisation.

5.21. Some example limits are calculated below for CBD oil, drinks and chocolate bars (Table 2). Given the lack of evidence of the consumption of large amounts of a CBD product to obtain the psychoactive effects, the group have calculated limits assuming the user consumes a single serving of these products for the claimed wellbeing effect. These limits have been calculated on the basis of what the Working Group thought was a normal amount to be consumed, however, this has been done for illustrative purposes and would need to be performed on a product by product basis.

Product	Weight of serving (g)	Δ^9-THC limit (w/w)	Δ^9-THC limit (% w/w)
Oil	0.45 (0.5 ml)	1.1×10^{-4}	0.011 (1.1×10^{-2})
Drink	524 (500 ml)	9.5×10^{-8}	0.0000095 (9.5×10^{-6})
Chocolate bar	100	5×10^{-7}	0.00005 (5×10^{-5})

Table 2: Guide limits for three common consumer CBD products containing 50 micrograms Δ^9-THC

5.22. These typical limits are feasible for industry to achieve using an isolate containing 0.03% Δ^9-THC (as a percentage of CBD content) with the appropriate level of dilution.

5.23. Although testing can theoretically achieve a level of quantification of 1.1×10^{-7} % (Defence Science and Technology Laboratory report, 2020b) the current testing capacities might not be able to achieve this in all product types (see 4. Analytical

Techniques and Annex C). Therefore, there would need to be investment within analytical testing to check these levels.

6. Conclusions

6.1. Extraction of controlled phytocannabinoids from consumer CBD products is unlikely to be a viable means of obtaining these drugs for illicit use.

6.2. It would be appropriate to set specific limits for the content of Δ^9-THC and its precursor Δ^9-THCA (i.e. Δ^9-THCA-A and Δ^9-THCA-B) in consumer CBD products.

6.3. Plant-derived consumer CBD products would not contain sufficient controlled phytocannabinoids (other than Δ^9-THC) or their precursor acids to produce any pronounced psychoactive effects unless they were added to the product (i.e. spiked). To prevent the possibility of spiking a limit should be set for all controlled phytocannabinoids in consumer CBD products.

6.4. The dose limit for total Δ^9-THC (Δ^9-THC plus Δ^9-THCA) should be 50 micrograms (µg) in a unit of consumption (where a unit of consumption or 'single serving' is the typical quantity of a CBD product consumed on one occasion).

6.5. At the recommended levels the controlled phytocannabinoids present in consumer CBD products are highly unlikely to produce any harmful effects.

6.6. Setting a single concentration limit that applies to all consumer CBD products would not be appropriate.

6.7. Further research is needed to confirm whether conversion of CBD to Δ^9-THC by extreme heating can occur and its relevance to the processes involved in CBD vaping evaluated.

6.8. Currently the methods for extraction, separation and quantification of controlled phytocannabinoids in consumer CBD products are not sufficiently robust with regards to sensitivity, accuracy and reproducibility.

6.9. Laboratories assessing compliance should be accredited to the ISO standard and producers should use laboratories which hold that accreditation to perform their quality assessment testing.

7. Recommendations

The ACMD make the following recommendations to provide a legal framework to control the amounts of phytocannabinoids in consumer CBD products under the MDA.

Recommendation 1

That the total dose of Δ^9-THC (including Δ^9-THCA, as calculated using Equation 1) and all other controlled phytocannabinoids in consumer CBD products be controlled. The dose of each controlled phytocannabinoid should not exceed 50 micrograms (µg) per unit of consumption.

Note 1. A unit of consumption or 'single serving' being defined as the typical quantity of a CBD product consumed on one occasion.

Lead organisations: Home Office.

Measure of impact: This will have been implemented by a change to the Misuse of Drugs Regulations 2001 (MDR).

Recommendation 2

That regulatory authorities ensure that any consumer CBD product permitted to market has limits on the content of controlled phytocannabinoids such that the dose of Δ^9-THC (including its precursor Δ^9-THCA) and of each of the other controlled phytocannabinoids does not exceed 50 micrograms (µg) per unit of consumption.

Lead organisations: Home Office liaising with the appropriate regulatory authorities and their devolved counterparts where appropriate:

- Food Standards Agency (FSA)
- Department for Business, Energy and Industrial Strategy (BEIS): (Office for Product Safety and Standards (OPSS)
- Department for Health and Social Care (DHSC): Office for Health Improvement and Disparities (OHID); and,
- Department for Environment Food and Rural Affairs (DEFRA) (UK REACH)

Measure of impact: Evidence of compliance with the permitted levels. The ACMD advise another analysis of the controlled phytocannabinoid content of consumer CBD products is performed by Dstl two years after the implementation of the regulations to check the level of compliance.

Recommendation 3

A further inter laboratory comparison trial (ring trial) should be commissioned specifically to support the capability of testing laboratories to detect controlled phytocannabinoids below the recommended maximum levels in a representative range of consumer CBD products

Lead organisations: Home Office

Measure of impact: An assessment of whether the necessary level of accuracy can be achieved in practice.

Recommendation 4

That development of more accurate testing for controlled phytocannabinoids is supported (as outlined in Notes 1 – 3 below) to allow testing capabilities to develop and be fully regulated.

Note 1: Standardised protocols should be developed for the extraction, separation and quantification of controlled cannabinoids (and their precursor acids) from consumer CBD products. These must be of sufficient reproducibility and sensitivity to be appropriate for the measurement of the level of controlled phytocannabinoids as recommended in this report.

Note 2: As chemical reference standards are not currently commercially available for all controlled phytocannabinoids, suppliers of chemical reference materials should be encouraged to produce certified standards for those controlled cannabinoids for which standards are not currently available.

Note 3: ACMD supports the recommendation from the Dstl report (Defence Science and Technology Laboratory report, 2020b) that the analytical methods used should be accredited to ISO 17025:2017 to ensure appropriate method validation, quality control and independent assessment of the methods.

Lead organisations: Home Office.

Measure of impact: An increase in the number of laboratories that have been, or are in the process of becoming, accredited to demonstrate their capability to quantify Δ^9-THC and related controlled phytocannabinoids in CBD products.

Annex A List of abbreviations used in this report

Abbreviation	Name
Δ^9-THCA	*trans*-delta-9-tetrahydrocannabinol-C5 acid
Δ^9-THCA-A/B	*trans*-delta-9-tetrahydrocannabinol-C5 Acid 2/4-carboxylic acid
ACMD	Advisory Council on the Misuse of Drugs
BEIS	Department for Business, Energy & Industrial Strategy
CB_1 receptor	Cannabinoid type-1 receptor
CB_2 receptor	Cannabinoid type-2 receptor
CBC(A)	Cannabichromene (Acid)
CBD(A)	Cannabidiol (Acid)
CBG(A)	Cannabigerol (Acid)
CBN	Cannabinol-C5
DEFRA	Department for Environment, Food and Rural Affairs
DHSC	The Department of Health and Social Care
Dstl	Defence Science and Technology Laboratory
FSA	Food Standards Agency
g	Gram (weight)
GC	Gas Chromatography
INCB	International Narcotics Control Board
LC	Liquid Chromatography
LoQ	Limit of Quantification
MDA	Misuse of Drugs Act 1971
MDR	Misuse of Drugs Regulations 2001
µg	Microgram (0.000001 g = 1 x 10^{-6} g)
mg	Milligram (0.001 g = 1 x 10^{-3} g)
MS	Mass Spectrometry

Abbreviation	Name
MS-MS	Tandem Mass Spectrometry
OHID	Office for Health Improvement and Disparities (formerly Public Health England)
OPSS	Office for Product Safety and Standards
PSA	Psychoactive Substances Act 2016
SCRA	Synthetic cannabinoid receptor agonists
THC(A)	Tetrahydrocannabinol (Acid)
THCV	Delta-9-Tetrahydrocannabivarin
UK	United Kingdom
UK REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
UNODC	United Nations Office on Drugs and Crime
US	United States

Annex B Quality of Evidence

Range of evidence

Evidence gathered was considered in line with the ACMD's 'Standard Operating Procedure for using evidence in ACMD reports' (ACMD, 2020).

The report mainly referred to peer-reviewed scientific literature, government reports (UK and international), a call for evidence carried out by the ACMD (ACMD, 2021) and past ACMD reports. To understand the CBD market better, the Working Group received information from representatives from the Defence Science and Technology Laboratory (Dstl), the Government Chemist's Team and representatives of industry. To understand the current legislation the Working Group had discussions with representatives from the Home Office, Food Standards Agency, Department for Business Energy and Industrial Strategy, the Department for Health and Social Care and the Department for Environment, Food and Rural Affairs.

Quality of this Evidence

There is limited literature about the controlled phytocannabinoids outside of Δ^9-THC, however, there is evidence about the effects of Δ^9-THC on humans**.**

The Dstl reports gave good insight into the theoretical testing capacity of different methods, however, there was poor evidence about what could be achieved in practice (Defence Science and Technology Laboratory report, 2020a), (Defence Science and Technology Laboratory report, 2020b). This was further complicated by the need to extract from different matrices. The main evidence for the practical capacity for the analytics industry to test was the Government Chemist's Team ring trial (Government Chemist's Team, 2021).

The call for evidence carried out by the ACMD received 14 responses, mainly from industry but also interested members of the public. The quality of this evidence ranged from full reports backed up by peer-reviewed literature to subjective opinion. This was all considered by the Working Group. The Working Group also considered the small sample size.

Evidence relevant to recommendations

Whilst there was evidence about the quantity of Δ^9-THC to produce a psychoactive effect this was when only consuming Δ^9-THC not with other phytocannabinoids. However, the international comparison gave the Working Group confidence in Recommendation 1 and Recommendation 2. The results of the ring trial and the Dstl reports back the need for Recommendation 3 and Recommendation 4.

Annex C Analytical Methods

The following is a summary table of analytical techniques taken from the Defence Science and Technology report (2020b). Following this is a description of these techniques.

Technique	Properties: advantages	Properties: disadvantages	Average LoQ of cannabinoids (mg/kg)	Average LoQ of cannabinoids (w/w %)
GC-FID	Low cost, simple and reproducible technique	Low sensitivity, cannot measure thermally labile acid form cannabinoids without derivatisation (decarboxylation occurs in hot GC inlet).	3,500	0.35
GC-MS (Direct)	High selectivity and sensitivity	High cost. Cannot measure thermally labile acid form cannabinoids without derivatisation (decarboxylation occurs in hot GC inlet).	0.46	0.000046 (4.6×10^{-5})
GC-MS (Derivatisation)	High selectivity and sensitivity	High cost. Trace level conversion of CBD to THC possible under acidic conditions. Difficult to disprove because of lack of THC-free matrix.	0.375	0.0000375 (3.75×10^{-5})
GC-MS/MS	Very high selectivity and sensitivity	Very high cost, derivatisation required for highest sensitivity can be inconsistent and compromise quantitative analysis. Expensive isotopically labelled reference chemicals required for accurate quantitation.	0.0011	0.00000011 (1.1×10^{-7})
LC-UV	Low cost, moderate to high sensitivity, selective for both acidic and neutral cannabinoids	Less selective than mass spectrometry and subject to matrix effects in complex samples.	27.59	0.002759 (2.759×10^{-3})
LC-MS	High selectivity and sensitivity High cost.	May requires longer methods to facilitate proper resolution between compounds that co-elute as a result of less MS selectivity than tandem mass spectrometry.	N/A	N/A
LC-MS/MS	Very high selectivity and sensitivity	Very high cost, matrix matching important for quantitative analysis and assessment of ion suppression in validation. Expensive isotopically labelled reference chemicals required for accurate quantitation.	0.004	0.0000004 (4×10^{-7})

Table 3: Summary table of analytical techniques. (Table 2 from (Defence Science and Technology Laboratory report, 2020b))

Below is a description of these techniques.

Gas-chromatography (GC)

A gas-chromatograph comprises a long, narrow, tube coated on the inside with a thin film of non-volatile liquid, known as the stationary phase. The tube, referred to as the analytical column, is coiled and heated in an oven. A small aliquot of a solvent extract is injected into one end of the heated column via a heated inlet which immediately vaporises the extract. A carrier gas, typically helium, hydrogen or nitrogen, flows through the column taking with it the evaporated extract. The compounds present in the extract will emerge from the other end of the column at different times (known as retention times) depending on their volatility and interaction with the stationary phase. Compounds are identified by comparing their retention time with those of reference standards.

GC is only suitable for compounds that are soluble and can be vaporised or converted to a volatile compound by derivatisation. It is not suitable for thermally labile compounds (e.g. THCA).

Several different methods can be used to detect the separated compounds as they emerge from the end of the GC column.

Gas-chromatography with Flame Ionisation detection (GC-FID)

The effluent from the end of the column is passed through a small hydrogen-air flame. When a compound emerges from the column and burns in the flame it produces ions which are detected as an electrical current. The current produced is proportional to the amount of compound being burnt. GC-FID can therefore be used to quantify the concentration of a compound in the extract by comparison of a reference standard of known concentration. However, the specificity of GC-FID is limited, as compounds are only identified by their retention time.

Gas-chromatography with Mass Spectrometry (GC-MS)

Mass spectrometry is a powerful analytical technique that can be used to identify compounds by elucidating their chemical structure. In GC-MS the effluent from the GC column enters the mass spectrometer where molecules of any compounds emerging from the GC column are bombarded with a beam of electrons. The collision will remove an electron from some of the molecules producing positively charged particles (ions) and some of these charged particles will break up into positively charged fragments of various sizes. A simple analogy would be a china cup which will break up into several characteristic pieces (handle, base, rim, etc) when dropped on the floor. The mass spectrometer then uses electric and magnetic fields in a ‘mass analyser’ to measure the size (“weight”) of each of the positively charged particles. An ion detector such as an electron multiplier is then used to detect the charged particles of each size. The results can be displayed as a mass spectrum on a chart showing the relative signal intensities of the detected ions. The mass spectrum can then be used to identify the parent compound by comparison with a library of mass spectra of reference compounds. The fragmentation pattern can also be used to elucidate the chemical structures of unknown compounds. The detector response for each

fragment size is proportional to the concentration of the parent compound and therefore GC-MS can also be used to quantify the concentration of the compound in the extract.

Gas-chromatography with Tandem Mass Spectrometry (GC-MS/MS)

The tandem mass spectrometer consists of two mass analysers coupled together. Sample extracts are analysed in the same way as GC-MS but selected charged particles of a particular size from the first mass analyser are made to split into smaller fragment ions. The size and abundance of these 'daughter ions' are then measured in a second mass analyser. These mass transition from a selected fragment ion to daughter ions provides greater confidence in the identification of unknown compounds. GC-MS/MS is useful for complex matrices and low-level quantitation.

Liquid Chromatography (LC)

Liquid chromatography, also referred to a high pressure or high-performance chromatography (HPLC), is based on the partition of compounds between a solid stationary phase and a liquid mobile phase. It comprises a chromatography column made from a short stainless-steel tube (typically 30-300mm long and 6mm outside diameter) packed with very small particles (typically 5µm diameter) of a stationary phase, such as silica or chemically modified silica. A mobile phase, typically a mixture of solvents such as water and acetonitrile and/or methanol, is forced through the column at a regulated rate using a high-pressure pump. A small aliquot of the solvent extract is injected into the mobile phase which carries the sample onto the column. Compounds present in the extract will emerge from the end of the column at different times (known as the retention time) depending on the strength of their attraction to the stationary phase.

Advantages of LC are that it can be used for non-volatile and thermally labile compounds, such as THCA, which are not suitable for GC analysis.

Several different methods can be used to detect the separated compounds as they emerge from the end of the LC column.

Liquid Chromatography with UV (LC-UV)

LC-UV is useful for the detection of compounds which have an absorption spectrum in the ultra-violet (UV) region such as those that contain pi-bonds as found in aromatic rings, carbonyl groups and double bonds. The phytocannabinoids all contain an aromatic ring so can be analysed by LC-UV.

In an LC-UV detector the effluent from the LC column passes through a transparent flow cell located in a beam of UV light of a fixed wavelength. The mobile phase does not absorb much UV light so when a compound emerges from the column it will absorb some of the UV light producing a peak in the chromatogram. Early LC-UV detectors used a mercury lamp for the light source which emits UV light at a fixed wavelength of 254 nm. More recently LC-UV detectors use a deuterium discharge lamp as it provides an almost continuous spectrum of light over the 190–400 nm range. A diffraction grating is then used to select a suitable wavelength for the compounds being analysed. In both cases, the amount of UV light

passing through the flow cell is measured using a photodiode and compared to the amount of UV light entering the flow cell.

The specificity of LC-UV detection at a fixed wavelength is limited as many compounds have an absorption in the ultraviolet region so compounds are only identified by their retention time.

The sensitivity of UV detection depends on how much UV light a standard solution of the compound absorbs (the molar extinction coefficient). The amount of UV light absorbed is proportional to concentration so LC-UV can be used for the quantitation of compounds by comparing the response with reference standards of known concentration.

Liquid Chromatography with Photodiode Array/Diode Array Detection (LC-UV/DAD)

The specificity of the LC-UV detector is greatly improved by measuring the absorption of UV light at more than one wavelength. In a (photo)diode array detector (DAD or PAD) light from the deuterium discharge lamp is shone directly onto the flow cell and UV light passing through the flow cell is dispersed by a diffraction grating (in the same way that a prism splits visible light into different colours). The amount of dispersed UV-light at each wavelength is measured simultaneously using an array of, typically 1024, photodiodes. The diode array detector can therefore record the complete UV spectrum of each compound emerging from the LC column, which considerably enhances the specificity. However, a disadvantage of LC-UV/DAD is that it is less sensitive than the fixed wavelength LC-UV detector. This is because the photodiodes in a diode array are much smaller than the single photodiodes used in a fixed wavelength UV detector and so receive less light.

Liquid Chromatography with Mass Spectrometry and Tandem Mass Spectrometry (LC-MS and LC-MS/MS)

These techniques are analogous to the corresponding GC-MS and GC-MS/MS techniques, the main difference being the interface between the LC column and the inlet of the Mass Spectrometer. The development of LC-MS was limited for many years due to the incompatibility of the MS electron beam ionisation process, which takes place in a vacuum, with a continuous liquid stream emerging from the LC column. This problem was overcome in the 1980's by the development of the electrospray ion source. The effluent from the LC column passes through a metal capillary maintained at a high voltage (3 – 5kV). The liquid is then nebulised at the tip of the capillary to form a fine spray of charged droplets. The solvent in these droplets rapidly evaporates and the residual electrical charge is transferred to the analyte to create molecular ions. These ions are then transferred into the high vacuum of the mass spectrometer via a series of small apertures and electric fields.

Electrospray ionisation (ESI) transfers relatively little energy to the analyte molecules, so little fragmentation occurs. LC-MS is therefore less specific than GC-MS as the mass spectrum contains less structural information than for GC-MS.

A further issue with ESI is ion suppression, which can occur when more than one component elutes simultaneously and are present in the same spray droplets. This can result in the electric charge being preferentially transferred to one of the components, suppressing the ions of the other component(s). This can be a limitation on the sensitivity of LC-MS and can lead to unreliable quantitative results. Stable isotope labelled internal

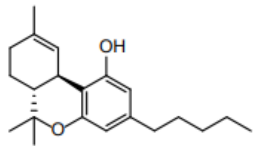
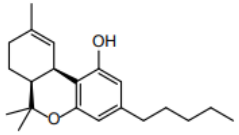
reference standards can be used to overcome the quantitation problem, otherwise sample preparation methods need to be developed to minimise the effects of ion suppression.

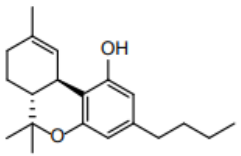
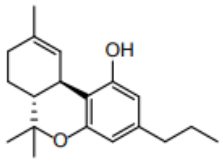
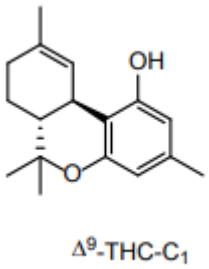
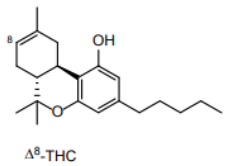
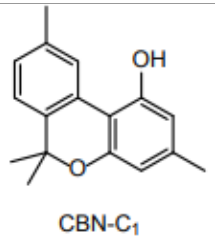
Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS)

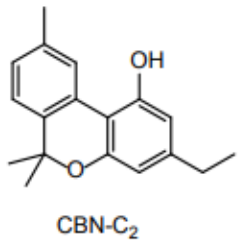
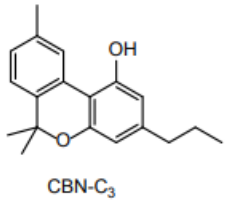
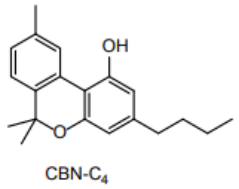
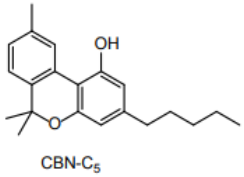
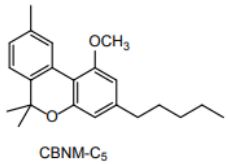
In tandem mass spectrometry, the ions produced by ESI can be induced to undergo more extensive fragmentation by collisions with an inert gas such as nitrogen or argon in a collision cell located between two mass analysers. The fragments can then be characterised in the second mass analyser. This is analogous to the GC-MS/MS technique and provides greater confidence in identifications.

Annex D Controlled Phytocannabinoids information

This table contains information on the 12 controlled phytocannabinoids identified in the ACMD's Phytocannabinoids report (ACMD, 2016) with additional technical information provided to us by the Laboratory of Government Chemist and the Working Group.

IUPAC Name	Synonyms	Structure	CAS Number	Sufficient evidence of psychoactivity (ACMD, 2016)?	Consider psychoactive?	Dose producing no psychoactive effect	Reference Standards
(-)(6aR,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol (+)(6aS,10aS)-6,6,9-Trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol	Dronabinol, (±)*Trans*-delta-9-Tetrahydrocannabinol, (±)delta-9-THC	 *trans*-Δ^9-THC-C_5	(-) 1972-08-3 (+) 17766-02-8	Yes	Yes	1 mg	Yes
(-) (6aS,10aR)-6,6,9-Trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol (+)(6aR,10aS)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol	(±) *Cis*-delta-9-tetrahydrocannabinol	 *cis*-Δ^9-THC-C_5	(-) 43009-38-7 (+) 69855-10-3	No	Unknown	N/A	Yes

(6aR,10aR)-3-butyl-6,6,9-trimethyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol	*nor*-THC, delta-9-tetrahydrocannabibutol, delta-9-THC-butyl, delta-9-THC-C4, THCB		60008-00-6	No	Unknown	N/A	Yes
(6aR,10aR)-6,6,9-trimethyl-3-propyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol	delta9-Tetrahydrocannabivarin, THCV		31262-37-0	Unclear	Unclear	10 mg	Yes
(6aR,10aR)-3,6,6,9-tetramethyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol	delta1-tetrahydrocannabiorcol, delta-9-tetrahydrocannabinol-C1, delta-9-THC-C1, delta-9-tetrahydrocannabiorcol		22972-65-2	No	Unknown	N/A	Yes
(6aR,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,10,10a-tetrahydro-6H-benzo[c]chromen-1-ol	delta-8-tetrahydrocannabinol		5957-75-5	Yes	Yes	Not enough evidence	Yes
3,6,6,9-Tetramethyl-6H-benzo[c]chromen-1-ol	Cannabinol-C1, cannabiorcol, CBN-C1			No	Unknown	N/A	Not currently

6,6,9-trimethyl-3-ethyl-6H-benzo[c]chromen-1-ol	Cannabinol-C2, CBN-C2			No	Unknown	N/A	Not currently
6,6,9-trimethyl-3-propyl-6H-benzo[c]chromen-1-ol	Cannabinol-C3, CBN-C3, cannabivarin		33745-21-0	No	Unknown	N/A	Yes
6,6,9-trimethyl-3-butyl-6H-benzo[c]chromen-1-ol	Cannabinol-C4, CBN-C4			No	Unknown	N/A	Not currently
6,6,9-trimethyl-3-pentyl-6H-benzo[c]chromen-1-ol	Cannabinol, cannabinol-C5, CBN		521-35-7	Yes	Yes	50 mg	Yes
1-methoxy-6,6,9-trimethyl-3-pentyl-6H-benzo[c]chromene	Cannabinol monomethyl ether, cannabinol methyl ether, CBNM-C5		41935-92-6	No	Unknown	N/A	Yes

Annex E ACMD membership, at time of publication

Professor Judith Aldridge	Professor of Criminology, University of Manchester
Dr Kostas Agath	Consultant Psychiatrist (addictions), Change Grow Live Southwark
Professor Owen Bowden-Jones	Chair of ACMD, Consultant psychiatrist, Central North West London NHS Foundation Trust
Dr Anne Campbell	Lecturer in social work, Queens University Belfast
Mr Mohammed Fessal	Chief Pharmacist, Change Grow Live
Dr Emily Finch	Clinical Director of the Addictions Clinical Academic Group and a consultant psychiatrist for South London and Maudsley NHS Trust
Professor Sarah Galvani	Professor of Social Research and Substance Use, Manchester Metropolitan University
Lawrence Gibbons MBE	Head of Drug Threat (Intelligence Directorate, Commodities), National Crime Agency
Professor Graeme Henderson	Professor of Pharmacology, University of Bristol
Dr Hilary Hamnett	Senior Lecturer in Forensic Science, University of Lincoln
Dr Carole Hunter	Lead pharmacist at the alcohol and drug recovery services, NHS Greater Glasgow and Clyde
Professor Roger Knaggs	Associate Professor in Clinical Pharmacy Practice, University of Nottingham
Professor Tim Millar	Professor of Substance Use and Addiction Research Strategy Lead, University of Manchester
Mr Rob Phipps	Former Head of Health Development Policy Branch, Department of Health, Social Services and Public Safety, Northern Ireland
Harry Shapiro	Director, DrugWise
Dr Richard Stevenson	Emergency Medicine Consultant, Glasgow Royal Infirmary
Dr Paul Stokes	Reader in Mood Disorders and Psychopharmacology, King's College London

Dr Ann Sullivan	Consultant physician in HIV and Sexual health and National co-lead for HIV Surveillance, Office for Health Improvement and Disparities
Professor Matthew Sutton	Chair in Health Economics, University of Manchester
Professor David Taylor	Professor of Psychopharmacology, King's College, London and Director of Pharmacy and Pathology, South London and Maudsley NHS Foundation Trust
Professor Simon Thomas	Consultant physician and clinical pharmacologist, Newcastle Hospitals NHS Foundation Trust and Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Dr Derek Tracy	Medical Director, West London NHS Trust
Ms Rosalie Weetman	Public Health Lead (Alcohol, Drugs and Tobacco), Derbyshire County Council - (currently on secondment to Office for Health Improvement and Disparities, as Programme Manager, Drug and Alcohol Improvement Support Team)
Dr David Wood	Consultant physician and clinical toxicologist, Guys and St Thomas' NHS Trust

Annex F Membership of the ACMD's Consumer CBD products Working Group

This report has been produced by the Consumer CBD products Working Group, with support from the Advisory Council on the Misuse of Drugs (ACMD) Secretariat.

ACMD Members:

Lawrence Gibbons MBE	Head of Drug Threat (Intelligence Directorate, Commodities) at National Crime Agency
Professor Graeme Henderson	(Working Group Chair) Professor of Pharmacology, University of Bristol
Professor Roger Knaggs	Associate Professor in Clinical Pharmacy Practice, University of Nottingham

Co-opted Members:

Professor Stephen Alexander	Associate Professor of Molecular Pharmacology, University of Nottingham
Dr Tom Freeman	Director of the Addiction and Mental Health Group (AIM), University of Bath
Professor Simon Gibbons	Professor of Natural Product Chemistry, UEA School of Pharmacy
Ric Treble MBE	Formerly Chief Forensic Scientist at LGC Forensics
Dr Mike White	Forensic Chemist

References

Abrams, D., Vizoso, H., Shade, S., Jay, C., Kelly, M., & Benowitz, N. (2007). 'Vaporization as a smokeless cannabis delivery system: a pilot study'. *Clinical Pharmacology & Therapeutics,* 82, pp 572-8.

ACMD. (2016, December 16). 'Plant cannabinoids: ACMD report'. Retrieved 06 07, 2021, from https://www.gov.uk/government/publications/plant-cannabinoids-acmd-report

ACMD. (2020). 'Standard Operating Procedure for using evidence in ACMD reports'. Retrieved from Advisory Council on the Misuse of Drugs: https://www.gov.uk/government/publications/standard-operating-procedure-for-using-evidence-in-acmd-reports

ACMD. (2021). 'Consumer cannabidiol (CBD) products: call for evidence'. Retrieved from Advisory Council on the Misuse of Drugs: https://www.gov.uk/government/news/commercial-cannabidiol-cbd-products-call-for-evidence

Ballard, M. E., & de Wit, H. (2011). 'Combined effects of acute, very-low-dose ethanol and delta(9)-tetrahydrocannabinol in healthy human volunteers'. *Pharmacology Biochemistry and Behavior*, 97, pp 627-31.

Beal, J. E., Olson, R., Laubenstein, L., Morales, J. O., Bellman, P., Yangco, B., Levkowitz L., Plasse, T. F., Shepard, K. V. (1995). 'Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS'. *Journal of Pain and Symptom Management*, 10, pp 89-97.

Beal, J. E., Olson, R., Lefkowitz, L., Laubenstein, L., Bellman, P., Yangco, B., Morales, J. O., Murphy, R., Powderly, W., Plasse, T. F., Mosdell, K. W., Shepard, K. V. (1997). 'Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia'. *Journal of Pain and Symptom Management*, 14, pp 7-14.

Cas, M. D., Eleonora, C., Saccardo, A., Arnoldi, S., Young, C., Scotti, S., de Manicor, E, V., Gambora, V., Roda, G. (2020). 'The Italian panorama of cannabis light preparation: Determination of cannabinoids by LC-UV'. *Forensic Science International*, 307, pp 110113. PMID: 31927249.

Chandra, S., Radwan, M., Majumdar, C., Church, J., Freeman, T., & ElSohly, M. (2019). 'New trends in cannabis potency in USA and Europe during the last decade (2008–2017)'. *European Archives of Psychiatry and Clinical Neuroscience*, 269, pp 5-15.

Chesher, G. B., Bird, K. D., Jackson, D. M., Perrignon, A., & Starmer, G. A. (1990). 'The effects of orally administered Δ^9-tetrahydrocannabinol in man on mood and performance measures: a dose-response study'. *Pharmacology Biochemistry and Behavior*, 35, pp 861-4.

Chesney, E., McGuire, P., Freeman, T. P., Strang, J., & Englund, A. (2020). 'Lack of evidence for the effectiveness or safety of over-the-counter cannabidiol products'. *Therapeutic Advances in Psychopharmacology*, 10, pp 1–13. doi: 10.1177/2045125320954992.

Citti, C., Linciano, P., Russo, F., Luongo, L., Iannotta, M., Maione, S., Laganà, A., Capriotti, A., L., Forni, F., Vandelli, M. A., Gigli G., Cannazza, G. (2019). 'A novel phytocannabinoid isolated from Cannabis sativa L. with an in vivo cannabimimetic activity higher than Δ^9-tetrahydrocannabinol: ∆9-Tetrahydrocannabiphorol'. *Scientific Reports* 9, pp 20335. doi: 10.1038/s41598-019-56785-1.

Cogan, P. S. (2020). The 'entourage effect' or 'hodge-podge hashish': the questionable rebranding, marketing, and expectations of cannabis polypharmacy. *Expert review of Clinical Pharmacology*, 13, pp 835-845.

Czégény, Z., Nagy, G., Babinszki, B., Bajtel, Á., Sebestyén, Z., Kiss, T., Csupor-Löffler, B., Tóth, B., Csupor, D. (2021). 'CBD, a precursor of THC in e-cigarettes'. *Scientific Reports* 11, pp 8951. doi: 10.1038/s41598-021-88389-z.

Defence Science and Technology Laboratory report. (2020a). 'Chemical analysis of cannabidiol (CBD) Products'. *DSTL/CR120711*.

Defence Science and Technology Laboratory report. (2020b). 'A review of analytical techniques and methods for the analysis of cannabidiol (CBD) products'. *DSTL/CR123172*.

Dubrow, G. A., Pawar, R. S., Srigley, C., Sam, J. F., Talavera, C., Parker, C. H., & Noonan, G. O. (2021). 'A survey of cannabinoids and toxic elements in hemp-derived products from the United States marketplace'. *Journal of Food Composition and Analysis*. 97, pp 103800. doi.org/10.1016/j.jfca.2020.103800.

Englund, A., Atakan, Z., Kralj, A., Tunstall, N., Murray, R., & Morrison, P. (2016). 'The effect of five day dosing with THCV on THC-induced cognitive, psychological and physiological effects in healthy male human volunteers: A placebo-controlled, double-blind, crossover pilot trial'. *Journal of Psychopharmacology*, 30, pp 140-51

European Monitoring Centre for Drugs and Drug Addiction (2019). 'Developments in the European cannabis market. Retrieved from Publications Office of the European Union', https://www.emcdda.europa.eu/system/files/publications/11391/TDAU19001ENN.pdf

Finlay, D. B., Sircombe, K. J., Nimick, M., Jones, C., & Glass, M. (2020). Terpenoids from cannabis do not mediate an entourage effect by acting at cannabinoid receptors. *Frontiers in Pharmacology*. 11, pp 359

Food Standards Agency. (2020). 'Food Safety Advice'. Retrieved August 02, 2021, from Cannabidiol: https://www.food.gov.uk/safety-hygiene/cannabidiol-cbd

Golombek, P., Müller, M., Barthlott, I., Sproll, C., & Lachenmeier, D. W. (2020). 'Conversion of cannabidiol (CBD) into psychotropic cannabinoids including tetrahydrocannabinol (THC): a controversy in the scientific literature'. *Toxics*. 8, pp 41

Government Chemist's Team. (2021, June 18). 'CBD and controlled cannabinoids: results from a ring trial'. Retrieved from https://www.gov.uk/government/news/cbd-and-controlled-cannabinnoids-results-from-a-ring-trial

Haney, M. (2007). 'Opioid antagonism of cannabinoid effects: differences between marijuana smokers and nonmarijuana smokers'. *Neuropsychopharmacology*, 32, pp 1391-403.

Heblinski, M., Santiago, M., Fletcher, C., Stuart, J., Connor, M., McGregor, I. S., & Arnold, J. C. (2020). 'Terpenoids commonly found in *Cannabis sativa* do not modulate the actions of phytocannabinoids or endocannabinoids on $TRPA_1$ and $TRPV_1$ channels'. *Cannabis and Cannabinoid research*, 5, pp 305-317.

Hollister, L. E., & Gillespie, H. K. (1973). 'Δ^8- and Δ^9-tetrahydrocannabinol comparison in man by oral and intravenous administration'. *Clinical Pharmacology & Therapeutics*. 14, pp 353-7

Karniol, I., Shirakawa, I., Takahashi, R., Knobel, E., & Musty, R. (1975). 'Effects of Δ^9-tetrahydrocannabinol and cannabinol in man'. *Pharmacology*, 13, pp 502-12.

Kinghorn, A., Falk, H., Gibbons, S., & Kobayashi, J. (2017). 'Phytocannabinoids: unraveling the complex chemistry and pharmacology of cannabis sativa'. Springer 2017, *Progress in the Chemistry of Organic Natural Products.*

Klumpers, L. E., Cole, D. M., Khalili-Mahani, N., Soeter, R. P., Beek, E. T., Rombouts, S. A., & Gerven, J. M. (2012). 'Manipulating brain connectivity with Δ^9-tetrahydrocannabinol: a pharmacological resting state FMRI study'. *Neuroimage*, 63, pp 1701-11.

Lachenmeier, D. W., Habel, S., Fischer, B., Herbi, F., Zerbe, Y., Bock, V., Rajcic de Rezende, T., Walch, S. G., & Sproll, C. (2019). Are side effects of cannabidiol (CBD) products caused by tetrahydrocannabinol (THC) contamination? *F1000Res*, 8, pp 1394

Laprairie, R. B., Bagher, A. M., Kelly, M. E., & Denovan-Wright, E. M. (2015). 'Cannabidiol is a negative allosteric modulator of the cannabinoid CB_1 receptor'. *British Journal of Pharmacology*. 172, pp 4790-805

Liebling, J.P., Clarkson, N.J., Gibbs, B.W., Yates, A.S., & O'Sullivan, S.E. (2020) **'**An analysis of over-the-counter cannabidiol products in the United Kingdom'. *Cannabis Cannabinoid Res*. doi: 10.1089/can.2019.0078. Online ahead of print.

Linciano, P., Cinzia, C., Russo, F., Tolomeo, F., Laganà, A., Capriotti, A., Luongo, L., Iannotta, M., Belardo, C., Maione, S., Forni, F., Vandelli, M. A., Gigli, G., Cannazza, G. (2019). 'Identification of a new cannabidiol n-hexyl homolog in a medicinal cannabis variety with an antinociceptive activity in mice: cannabidihexol'. *Scientific Reports*. 10, pp 22019. doi: 10.1038/s41598-020-79042-2.

Newmeyer, M. N., Swortwood, M. J., Abulseoud, O. A., & Huestis, M. A. (2017). 'Subjective and physiological effects, and expired carbon monoxide concentrations in frequent and occasional cannabis smokers following smoked, vaporized, and oral cannabis administration'. *Drug and alcohol dependence*, 175, pp 67-76.

Pavlovic, R., Nenna, G., Calvi, L., Panseri, S., Borgonovo, G., Giupponi, L., Cannazza, G., & Giorgi, A. (2018). 'Quality traits of "cannabidiol oils": cannabinoids content, terpene fingerprint and oxidation stability of european commercially available preparations'. *Molecules*. 23, pp 1230

Perez-Reyes, M., Timmons, M. C., Davis, K. H., & Wall, E. M. (1973). 'A comparison of the pharmacological activity in man of intravenously administered Δ^9-tetrahydrocannabinol, cannabinol, and cannabidiol'. *Experientia*. 29, pp 1368-69

Rzepa, E., Tudge, L., & McCabe, C. (2016). 'Resting-state functional connectivity following a single dose treatment with CB1 neutral antagonist tetrahydrocannabivarin (THCv) in healthy volunteers'. *The International Journal of Neuropsychopharmacology*. 19, pp 1-7

Santiago, M., Sachdev, S., Arnold, J. C., McGregor, I. S., & Connor, M. (2019). 'Absence of entourage: terpenoids commonly found in *Cannabis sativa* do not modulate the functional activity of Δ^9-THC at human CB_1 and CB_2 receptors'. *Cannabis and Cannbinoid research*. 4, pp 165-76

Tahir, M. N., Shahbazi, F., Rondeau-Gagné, S., & Trant, J. F. (2021). 'The biosynthesis of the cannabinoids'. *Journal of Cannabis Research*. 3, pp 7

Tham, M., Yilmaz, O., Alaverdashvili, M., Kelly, M. E., Denovan-Wright, E. M., & Laprairie, R. B. (2019). 'Allosteric and orthosteric pharmacology of cannabidiol and cannabidiol-dimethylheptyl at the type 1 and type 2 cannabinoid receptors'. *British Journal of Pharmacology*, 176, pp 1455-69

Tudge, L., Williams, C., Cowen, P., & McCabe, C. (2015). 'Neural effects of cannabinoid CB_1 neutral antagonist tetrahydrocannabivarin on food reward and aversion in healthy volunteers'. *International Journal of Neuropsychopharmacology*, 18: pyu094. doi: 10.1093/ijnp/pyu094.

UK Legislation. (2001). The Misuse of Drugs Regulations. Retrieved July 13, 2021, from https://www.legislation.gov.uk/uksi/2001/3998/contents

US legislation. (2018). Agricultural Improvement Act 2018. Retrieved from https://ecfr.federalregister.gov/current/title-7/subtitle-B/chapter-IX/part-990

Wang, M., Wang, Y.-H., Avula, B., Radwan, M. M., Wanas, A. S., Antwerp, J. v., Parcher, J. F., ElSohly, M., A. & Khan, I. A. (2016). 'Decarboxylation study of acidic cannabinoids: a novel approach using ultra-high-performance supercritical fluid chromatography/photodiode array-mass spectrometry'. *Cannabis and Cannabinoid Research*, 1, pp 262-71

Wang, Y.-H., Avula, B., ElSohly, M. A., Radwan, M. M., Wang, M., Wanas, A. S., Mehmedic, Z. & Khan, I. A. (2016). 'Quantitative determination of Δ^9-THC, CBG, CBD, their acid precursors and five other neutral cannabinoids by UHPLC-UV-MS'. *Planta Medica*, 84, pp 260-66.

Zuurman, L., Roy, C., Schoemaker, R. C., Hazekamp, A., Hartigh, J. d., Bender, J. C., Verpoorte, R., Pinquier, J., Cohen, A. & Van Gerven, J. M. (2008). Effect of intrapulmonary tetrahydrocannabinol administration in humans. *Journal of psychopharmacology*, 22, pp 707-16.